

# Dystonia and deep brain stimulation: correlation between genetic mutation and clinical outcome

Gloria Rožmarić<sup>1</sup>, Mario Hero<sup>1,2</sup>, Valentino Rački<sup>1,2</sup>, Eliša Papić<sup>1,2</sup>, Vladimira Vuletić<sup>1,2</sup>

<sup>1</sup> Clinic of Neurology, Clinical Hospital Center Rijeka, Rijeka, Croatia

<sup>2</sup> Department of Neurology, Faculty of Medicine, University of Rijeka, Rijeka, Croatia

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## Correspondence:

Vladimira Vuletić  
vladimira.vuletic@gmail.com

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## ABSTRACT

Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions, leading to abnormal involuntary movements or postures. Although the pathogenesis of dystonia is not entirely understood, lack of intracortical inhibition, aberrant sensory integration and derangement of neural plasticity are known to contribute. Etiologically, dystonia can be idiopathic, acquired or hereditary, most commonly occurring with TOR1A, THAP1, GCH1, and KMT2B mutations. The classification of dystonia is based on two main axes: clinical features (Axis I) and etiology (Axis II). When it comes to treatment a variety of therapeutic options are available, including oral medication therapy, intramuscular injections of botulinum neurotoxins (BoNTs), physical and occupational therapy and invasive neurosurgical treatment. Deep brain stimulation (DBS) is an established neurosurgical treatment for medication-refractory dystonia. As more evidence suggests that DBS treatment outcomes may be related to a hereditary basis, genotype determination is an important factor to consider in patient selection and prognostic counselling.

**KEYWORDS:** Dystonia; Deep Brain Stimulation; Genetics

## SAŽETAK

**DISTONIJA I DUBOKA MOZGOVNA STIMULACIJA: KORELACIJA IZMEĐU GENETSKE MUTACIJE I KLINIČKI ISHOD**  
Distonija je neurološki poremećaj pokreta karakteriziran trajnim ili povremenim kontrakcijama mišića, uzrokujući abnormalne nevoljne pokrete ili položaje. Iako patogeneza distonije nije u potpunosti razjašnjena, poznato je da nedostatak intrakortikalne inhibicije, abnormalna senzorna integracija i poremećaj neuroplastičnosti imaju bitnu ulogu u nastanku bolesti. Distonija može biti idiopatska, stečena ili nasljedna, a najčešći uzroci nasljednih oblika jesu mutacije TOR1A, THAP1, GCH1 i KMT2B gena. Klasifikacija distonije sistematizirana je na temelju dvije osnovne osi: klinička slika (os I) i etiologija (os II). Liječenje distonije uključuje oralnu terapiju lijekovima, intramuskularne injekcije botulinum toksina (BoNTs), fizikalnu i radnu terapiju te invazivno neurokirurško liječenje. Duboka mozgovna stimulacija (DBS) je zlatni standard liječenja u slučajevima kada pacijent ne odgovara na oralnu terapiju. Sve je više istraživanja koja ukazuju na to da ishodi liječenja DBS-a mogu biti povezani s genetskom osnovom, stoga je genotipizacija važan čimbenik pri odabiru pacijenata za spomenuto liječenje.

**KLJUČNE RIJEČI:** Distonija; Duboka mozgovna stimulacija; Genetika

## INTRODUCTION

Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions, leading to twisting, repetitive or patterned movements or abnormal postures (1). Dystonia can be idiopathic, acquired or hereditary, most commonly occurring with TOR1A, THAP1, GCH1, and KMT2B mutations (1). The classification of dystonia is based on two main axes: clinical features (Axis I) and etiology (Axis II) (2). Since the first dystonia gene was discovered, more than 40 genes have been connected to isolated, combined and complex hereditary dystonia forms. As knowledge in this area continues to advance, studies have shown that hereditary basis is associated with clinical outcomes, especially when it comes to advanced therapy such as deep brain stimulation (DBS).

## DYSTONIA

### DEFINITION AND CLASSIFICATION

Dystonia is a hyperkinetic movement disorder characterized by sustained or intermittent muscle contractions, leading to twisting, repetitive or patterned movements or abnormal postures. Dystonic movements are often triggered or worsened by voluntary action and associated with excessive muscle activation (1). Dystonia has distinct clinical features, but a wide range of phenomenological presentations. Therefore, a constructive classification is required to plan a rational diagnostic approach, to define the prognosis and determine the right therapy. The Movement Disorder Society expert members proposed a classification of dystonia among two main axes: clinical features and etiology. The Axis I provides specific clinical presentation categories such as age at onset, body distribution, temporal pattern and associated features (2). On the other hand, the Axis II addresses etiology with two dimensions pertaining to histopathological abnormalities or genetic contributions (2,3).

### PATHOGENESIS

The pathogenesis of dystonia is still not entirely understood, but it is based on three main abnormalities. The first one is lack of intracortical inhibition at various levels of the central nervous system which may cause the excess movement and overflow phenomenon (4). The aberrant intracortical inhibition may be present in both hemispheres, despite unilateral symptoms and even in asymptomatic body areas (5). The second is aberrant sensory integration. A deficiency in sensory or perceptual function, known as “sensorimotor integration,” is another prominent issue in the pathophysiology of dystonia, despite the fact that dystonia is often considered as a pure motor condition (4). The third is a derangement of neural plasticity. For instance, the task-specificity in focal dystonia points to a malfunction in the neural circuits responsible for encoding motor memories, which results in aberrant motor engrams. This may also explain the patterned muscular activation seen in dystonia (5). Finally, the understanding of

the complex molecular pathophysiology has been improved with the identification of novel genes.

### DIAGNOSIS AND TREATMENT

Diagnosis of dystonia is challenging due to variety of etiologies and clinical manifestations. Once a diagnosis is suspected, the first step is to exclude conditions that may resemble dystonia, known as pseudodystonia, which includes non-neurological disorders of the musculoskeletal system, disorders of sensory pathways, disorders of motor pathways and compensatory postures (6). The next step is to define the dystonic syndrome according to aforementioned classification. For patients with isolated dystonia, the laboratory evaluation is based on the patient's age at onset, body distribution and whether there are affected family members (7). In patients with hemidystonia or generalized dystonia, neuroimaging is beneficial due to possible structural causes (7). In sporadic adult-onset isolated dystonia genetic testing is performed if there are other affected family members (7). On the other hand, in childhood-onset dystonia there is a substantially higher rate of finding a cause. Diagnostics includes neuroimaging (MRI) and genetic testing (7). The method or technology chosen for genetic testing should be determined based on the clinical presentation at onset and the most recent examination, family history, availability of the particular diagnostic test, experience of the physician and other factors (8). Despite the aforementioned, the diagnosis relies mainly on clinical evaluation. There are no available objective biomarkers that can validate the diagnosis or track the development of symptoms (3).

The treatment of dystonia is primarily symptomatic, although some causes are amenable to specific therapies. There are a variety of therapeutic options available, including oral medication therapy, intramuscular injections of botulinum neurotoxins (BoNTs), physical and occupational therapy and invasive neurosurgical treatment (7). Chemodenervation with botulinum toxin is the preferred treatment method for focal or select-body regions in generalized and segmental dystonia (9). The most common oral pharmaceutical therapies for dystonia include acetylcholine-related drugs such as trihexyphenidyl, benzotropine, biperiden, ethopropazine, orphenadrine and procyclidine; dopamine-related drugs such as levodopa, pramipexole, ropinirole and tetrabenazine; gamma-aminobutyric acid-related drugs such as alprazolam, baclofen, chlordiazepoxide, clonazepam and diazepam; and muscle relaxants such as baclofen, benzodiazepines, carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol and orphenadrine (7). Other non-invasive methods include repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) (9). Ultimately, deep brain stimulation is an effective and disease-modifying surgical treatment for dystonia and will be discussed in the following paragraphs (10). Rehabilitation methods appear to further enhance benefits when combined with neuromodulation (9).

## GENETICS

Since the first dystonia gene was discovered nearly 25 years ago, more than 40 genes have been connected to isolated, combined and complex hereditary dystonia forms. The MDS Task Force for the Nomenclature of Genetic Movement Disorders proposed a new system of nomenclature that considers the causative gene rather than locus symbols and links the prefix to the primary phenotype (e.g., DYT 1 is known as DYT-TOR1A) (2). The prefix DYT is only used if dystonia is the primary disease feature as a result of a pathogenetic mutation, but if another movement disorder is present with dystonia, a double prefix would be assigned (e.g., DYT/PARK-ATP1A3) (11). The phenotypic spectrum is broad and the distribution can be focal (one affected body site), segmental (more than one contiguous/noncontiguous sites) or generalized (trunk and two other sites affected) (12). If dystonia predominates in the clinical picture, the isolated dystonia may be taken into consideration. The gene mutations include DYT-TOR1A, DYT-KMT2B, DYT-THAP1, DYT-ANO3, DYT-GNAL, DYT-HPCA, DYT-TUBB4A, DYT-PRKRA, and novel variants such as DYT-GNB1 (12,13). The majority of isolated dystonias have autosomal dominant inheritance (12). Regarding age of onset, DYT-TOR1A, DYT-KMT2B, DYT-THAP1, DYT-HPCA, DYT-TUBB4A and DYT-PRKRA are more likely to appear in infancy, childhood and adolescence, whereas DYT-ANO3 and DYT-GNAL appear in early adulthood (12). On the other hand, according to body distribution DYT-TOR1A, DYT-KMT2B, DYT-THAP1, DYT-HPCA and DYT-PRKRA are the most common causes of generalized dystonia, whereas DYT-TOR1A, DYT-KMT2B and DYT-HPCA typically begin asymmetrically in the lower limbs with secondary generalization (12). DYT-THAP1 may start at the upper half of the body, affecting the upper limbs and cranio-cervical regions causing speech issues, with subsequent generalization (14). DYT-GNAL and DYT-ANO3 are more likely to cause focal and segmental dystonia, they usually start at the cervical level and can cause a head tremor (12). Also, DYT-ANO3 is more likely to result in laryngeal dystonia and speech difficulties, along with subsequent generalization affecting the upper limbs at younger ages (12).

On the other hand, the presence of another movement disorder in addition to dystonia identifies as combined dystonia. Dystonia-parkinsonism is defined as the combination of parkinsonism and dystonia and has four monogenic subtypes: DYT/PARK-GCH1, DYT/PARK-TH, DYT/PARK-TAF1 and DYT/PARK-ATP1A3 (15). Combined dystonia has a distinct form of heredity, DYT/PARK-GCH1 and DYT/PARK-ATP1A3 exhibit autosomal dominant inheritance, DYT/PARK-TH exhibits autosomal recessive inheritance and DYT/PARK-TAF1 exhibits X-linked transmission (14). Furthermore, myoclonus-dystonia is caused by MYC/DYT-SGCE and MYC/DYT-KCTD17 gene mutation, it typically begins in the first decade of life and is characterized by generalized myoclonic jerks that occur predomi-

nantly in the neck and proximal upper limbs. In most patients dystonia is less prominent and the most prevalent symptoms are cervical dystonia and writer's cramp (15,16). Mutation in ADCY5 is responsible for childhood-onset chorea and dystonia, known as CHOR/DYT-ADCY5 (17). The disease is characterized by neck hypotonia and a myopathy-like facial appearance. Before the movement issue becomes persistent, episodic attacks may precede the disease and is frequently misdiagnosed as dyskinetic cerebral palsy (17).

Types of genetic testing for dystonia include diagnostic testing, carrier testing, predictive or presymptomatic testing and prenatal testing. Diagnostic testing is the most used because it helps to establish a genetic diagnosis in affected individuals (8). Carrier and predictive testing are similar. They are used for individuals suspected of carrying a pathogenic variant, these people are unaffected, but have a family history of dystonia (8). Finally, prenatal genetic testing is used to determine whether a fetus has a presumed disease-causing change before birth (8). The types of genetic tests available for dystonia include simple single-variant testing and single-gene Sanger sequencing to advanced next-generation sequencing (NGS) based approaches such as NGS gene panels, clinical exome sequencing (CES), whole-exome sequencing (WES) or whole-genome sequencing (WGS) (8). Copy number variation (CNV) analysis may be required in some cases. Which approach or technology will be used should be determined individually, as it depends on the clinical presentation at the time of onset and at the most recent examination, family history, availability of the specific diagnostic test and the physician's experience (8).

Different hereditary forms of dystonia are caused by defects in various genes, which leads to various pathophysiological pathways. As a result, identifying the relevant gene may have a big impact on the therapeutic management. None of the previously mentioned isolated forms respond to levodopa, but DYT-TOR1A, DYT-THAP1, DYT-ANO3, DYT-KMT2B and DYT-HPCA may respond to anticholinergics (12). Combined dystonia caused by DYT/PARK-GCH1, DYT/PARK-TH, DYT/PARK-TAF1 and DYT/PARK-ATP1A3 mutations has a good response to levodopa therapy (15). Furthermore, in case of myoclonus-dystonia, MYC/DYT-SGCE myoclonic symptoms respond to alcohol, whereas MYC/DYT-KCTD17 does not (15,16). Also, the response to DBS therapy varies according to the genetic mutation which will be discussed in "Genetics and deep brain stimulation" section.

In terms of a novel therapeutic approach, gene therapy would be an absolute game-changer. The medical application of therapies that can restore lost gene function via viral transgenic expression or mitigate the negative effect of abnormally functioning genes by neutralizing or modulating their mRNAs through antisense oligonucleotides or RNA interference is still being studied, and further research is needed (8).

## DEEP BRAIN STIMULATION

### DEFINITION AND MECHANISM OF ACTION

Deep brain stimulation is an established treatment for medication-refractory movement disorders. The DBS consists of intracranial electrode, implantable pulse generator (IPG) and connecting wires (18). During the implantation procedure, electrodes are placed within a specific deep brain structures. The subthalamic nucleus (STN) and the globus pallidus internus (GPi) are two common structures targeted by DBS in dystonia (19). The electrode is connected to the IPG by a connecting wire, which is insulated and passes under the skin of the head, neck and shoulders (18). The IPG, which houses the battery, is implanted in a previously created subcutaneous “pocket” in the pectoral region beneath the fatty tissue, or less frequently, under the pectoral muscle in the armpit area or under the skin of the abdomen (18). The neurostimulation consists of the stimulus amplitude (A), frequency (f) and pulse width (pw) and are adjusted according to the individual needs of each patient (18,20).

Despite clinical benefits, the exact mechanism underlying its effectiveness is not entirely understood and is still being debated (21). There are three main hypotheses regarding its mechanism. The first, known as the “inhibition hypothesis,” contends that DBS alleviates symptoms by directly inhibiting the surrounding neurons. The main premise is that loss of dopaminergic neurons increases the frequency of burst impulses from the STN and GPi, which can be inhibited by stimulating the aforementioned nuclei (22). The inhibitory effect can be attributed to a variety of mechanisms, including depolarization block, inactivation of sodium voltage channels and activation of inhibitory neurons (23). The second, known as the “excitation hypothesis,” considers that DBS achieves its effect through excitation and/or excitation-inhibition of the target nucleus via efferent pathways, or antidromic activation reaches the original region via afferent pathways (21). GPi-DBS has been shown to reduce bursts of electrical impulses from the thalamus in animal primate models and patients with dystonia by activating inhibitory projections (21). The third hypothesis, known as the “disruption hypothesis,” proposes that the DBS beneficial effects are caused by disrupting abnormal information flow through the GPi and STN (21). Since the increased frequency and abnormal patterns of electrical impulses in the basal ganglia are transmitted to the thalamus and motor cortex, which causes characteristic motor symptoms, inhibition of their transmission could alleviate motor symptom expression (21). Aside from the placement of the electrodes, it is important to emphasize the significance of adjusting their frequency. Namely, high-frequency stimulation of 100 Hz leads to an inhibitory response in brain cells, whereas low-frequency stimulation at 10Hz does not (24). The role of an implanted electrode is to redistribute sodium and chlorine ions throughout the extracellular space in order to generate an electric field that can regulate the voltage sensor of sodium channel proteins located in the membrane

of neuron (24). At the cellular level, the opening of sodium channels causes an action potential to propagate to the neuron's axon terminals in both orthodromic and antidromic directions (24). The stimulated axons are capable of following stimulation frequencies at 100Hz, but synaptic transmission does not. Under such high-frequency activity, axon terminals can deplete their neurotransmitters and postsynaptic receptors can decrease, making further signal transmission impossible (24). This process, known as “synaptic filtering”, may explain one of the main effects of DBS (24).

### CLINICAL OUTCOMES AND EFFICACY

The posteroventral lateral GPi has emerged as the most established target for DBS in dystonia, while additional targets that are under investigation include the STN and the thalamus (24,25). The long-term benefit of chronic DBS in dystonia is often delayed, requiring weeks or months to achieve optimal results. However, it has been shown that long-term stimulation appears to result in long-lasting changes in the brain, even though dystonia can recur within minutes to hours after stimulation has been turned off in the early postoperative period (24). This suggests that DBS may act as a disease-modifying treatment (24). The beneficial effects of GPi-DBS for cervical dystonia, segmental primary dystonia and generalized dystonia have been shown in several randomized sham-controlled trials. Volkmann et al. have reported that bilateral GPi-DBS decreased motor impairment and related disability in patients with medication-refractory cervical dystonia (26). Furthermore, Kupsch et al. have reported that patients with generalized and segmental dystonia, who received GPi-DBS, experienced a 39% movement score improvement, a 38% reduction in disability, a 30% improvement in the physical aspects of the quality of life and mood improvement without behavioral abnormalities (27). A long-term study by Kamel et al. have reported statistically significant improvement in Burke-Fahn-Marsden dystonia rating scale (BFMDRS) and Global Dystonia Severity scale (GDS) 6 and 12 months after the implantation procedure in patients with generalized and cervical dystonia (28). Additionally, they reported that the improvement was considerably better in patients with long-term DBS, lasting more than 5 to 7 years (28).

When comparing GPi-DBS and STN-DBS, studies have shown significant improvements in movement symptoms, disability symptoms, Beck Depression Inventory (BDI) scores and SF-36 score, without statistically significant difference between groups (19).

### GENETICS AND DEEP BRAIN STIMULATION

An increasing amount of evidence suggests that the outcomes of DBS treatment may be linked to a genetic cause, which is an important prognostic factor when selecting patients for DBS therapy. According to Artusi et al., GPi-DBS has a beneficial short- and long-term impact on motor and disability outcomes

in patients with DYT-TOR1A, DYT-THAP1 and NBIA/DYT-PANK2, unlike the other monogenic dystonias, with DYT-TOR1A showing the greatest improvement (29,30). The lower amount of motor improvement seen in NBIA/DYT-PANK2 may be due to the PKAN phenotype's variability in related features, such as spasticity (29). DYT-KMT2B responds effectively to GPi-DBS with much better outcome in males and those with more severe dystonia at baseline (31). Studies have suggested that the duration of dystonia prior to surgery may or may not predict clinical outcome after the implantation. Indeed, Isaias et al. have reported that the earlier surgical treatment in patients with DYT-TOR1A may be beneficial (32). Furthermore, comparing CHOR/DYT-ADCY5 to DYT-TOR1A, GPi-DBS benefits were significantly lower (29). On the contrary, DYT/PARK-TAF1 patients experienced significant motor and disability improvement, but DBS should be evaluated in the early stages of the disease because progressive neurodegeneration was associated with worse response (29,33). In patients with MYC/DYT-SGCE, GPi-DBS has been shown to benefit both myoclonus and dystonia, with slightly better improvement in myoclonus scores (34). Albanese et al. suggest that carrying ATP1A3 gene mutation may be a negative predictor for GPi-DBS since it did not have a beneficial

clinical outcome (35). There is significant variability in clinical outcomes in rare forms of dystonia and the need for more case reports to reach a valid conclusion.

## CONCLUSION

As more evidence suggests that DBS treatment outcomes may be related to a hereditary basis, genotype determination is an important factor to consider in patient selection and prognostic counselling. GPi-DBS showed both short- and long-term effectiveness in DYT-TOR1A, as well as a lower but still substantial improvement in DYT-THAP1 and NBIA/DYT-PANK2. GPi-DBS showed promising results in other isolated and combined dystonias, with the exception of ATP1A3 mutation where DBS did not provide beneficial results. Therefore, it is important to consider the genotype as a potential predictor of postoperative outcome. Additional research is required to illuminate the role of GPi-DBS in patients with rare genetic forms of dystonia.

## CONFLICT OF INTEREST STATEMENT:

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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